

CLAIMS

1. A method for inducing tolerance in a patient to a graft from a mismatched donor comprising the steps of T cell ablation, reactivation of the thymus, and administration, from the graft donor to the patient, of cells selected from the group consisting of hematopoietic stem cells, 5 epithelial stem cells, progenitor cells, and mixtures thereof.
2. The method of claim 1 wherein the patient's thymus has been at least in part deactivated.
3. The method of claim 2 wherein the patient is post-pubertal.
4. The method of claim 2 wherein the patient has or had a disease or treatment of the 10 disease that at least in part deactivated the patient's thymus.
5. The method of claim 3 wherein the treatment of the disease is through chemotherapy.
6. The method of claim 1 wherein the donor hematopoietic stem cells are CD34+.
7. The method of claim 1 wherein the hematopoietic stem cells are provided about 15 the time when the thymus begins to regenerate or shortly thereafter.
8. The method of claim 1 wherein the hematopoietic stem cells are provided at the time disruption of sex steroid mediated signaling to the thymus is begun.
9. The method of claim 1 wherein the method of disrupting the sex steroid mediated signaling to the thymus is through surgical castration to remove the patient's gonads.
- 20 10. The method of claim 1 wherein the method of disrupting the sex steroid mediated signaling to the thymus is through administration of one or more pharmaceuticals.

11. The method of claim 10 wherein the pharmaceuticals are selected from the group consisting of LHRH agonists, LHRH antagonists, anti-LHRH vaccines and combinations thereof.

12. The method of claim 11 wherein the LHRH agonists are selected from the group 5 consisting of Eulexin, Goserelin, Leuprolide, Dioxalan derivatives, Triptorelin, Meterelin, Buserelin, Histrelin, Nafarelin, Lutrelin, Leuprorelin and Deslorelin.

13. The method of claim 11 wherein the LHRH antagonist is Abarelix.

14. A kit for the improvement of graft acceptance in a patient comprising an LHRH analog, a group of stem or progenitor cells from the donor of the graft,

10 15. The kit of claim 14 wherein the LHRH analog is selected from the group consisting of one or more LHRH agonists, one or more LHRH antagonists, and combinations thereof.

16. The kit of claim 14 wherein the stem or progenitor cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

15 17. The kit of claim 14 further comprising a cytokine.

18. The kit of claim 17 wherein the cytokine is selected from the group consisting of interleukin 7, stem cell factor, interleukin 2, interleukin 15, granulocyte colony stimulating factor, keratinocyte growth factor, and combinations thereof.

19. A method for inducing tolerance in a post-pubertal patient to a graft from a 20 mismatched donor, comprising:

ablation of T cells of the patient;

reactivating the thymus of the patient; and

administering cells from the mismatched donor to the patient, the cells being selected from the group consisting of stem cells, progenitor cells, and combinations thereof.

wherein the patient has an increased induction of tolerance to the graft compared to an untreated patient.

5        20.      The method of claim 19, wherein the thymus of the patient has been at least in part atrophied before it is reactivated.

21.      The method of claim 20, wherein the patient has a disease that at least in part atrophied the thymus of the patient.

10       22.      The method of claim 20, wherein the patient has had a treatment of a disease that at least in part atrophied the thymus of the patient.

23.      The method of claim 19, wherein the thymus is reactivated by disruption of sex steroid-mediated signaling to the thymus.

24.      The method of claim 22, wherein the treatment of the disease is immunosuppression, chemotherapy, or radiation treatment.

15       25.      The method of claim 19, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

26.      The method of claim 19, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

20       27.      The method of claim 25, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

28.      The method of claim 25, wherein the cells are hematopoietic stem cells.

29.      The method of claim 28, wherein the hematopoietic stem cells are CD34+.

30. The method of claim 28, wherein the hematopoietic stem cells are administered when the thymus begins to reactivate.

31. The method of claim 23, wherein the cells are administered at the time disruption of sex steroid mediated-signaling to the thymus is begun.

5 32. The method of claim 23, wherein the sex steroid-mediated signaling to the thymus is disrupted by surgical castration.

33. The method of claim 23, wherein the sex steroid-mediated signaling to the thymus is disrupted by chemical castration.

10 34. The method of claim 23, wherein the sex steroid-mediated signaling to the thymus is disrupted by administration of one or more pharmaceuticals.

35. The method of claim 34, wherein the one or more pharmaceuticals is selected from the group consisting of LHRH agonists, LHRH antagonists, anti-LHRH vaccines, anti-androgens, anti-estrogens, SERMs, SARMs, SPRMs, ERDs, aromatase inhibitors, anti-progestogens, and combinations thereof.

15 36. The method of claim 35, wherein the LHRH agonists are selected from the group consisting of Eulexin, Goserelin, Leuprolide, Dioxalan derivatives, Triptorelin, Meterelin, Buserelin, Histrelin, Nafarelin, Lutrelin, Leuprorelin, Deslorelin, Cystorelin, Decapeptyl, Gonadorelin, and combinations thereof.

20 37. The method of claim 35, wherein the LHRH antagonists are selected from the group consisting of Abarelix, Cetrorelix, and combinations thereof.

38. The method of claim 19, further comprising administering at least one cytokine, at least one growth factor, or a combination of at least one cytokine and at least one growth factor to the patient.

39. The method of claim 19, wherein the cytokine is selected from the group consisting of Interleukin 2 (IL-2), Interleukin 7 (IL-7), Interleukin 15 (IL-15), and combinations thereof.

5 40. The method of claim 19, wherein the growth factor is selected from the group consisting of members of the epithelial growth factor family, members of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), and combinations thereof.

10 41. The method of claim 39, wherein the growth factor is selected from the group consisting of members of the epithelial growth factor family, members of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), and combinations thereof.

42. A kit for the improvement of graft acceptance in a patient, the kit comprising:  
an LHRH analog; and

15 cells from the donor of the graft, wherein the cells are selected from the group consisting of stem cells, progenitor cells, and combinations thereof.

43. The kit of claim 42, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

44. The kit of claim 42, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

45. The kit of claim 43, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

46. The kit of claim 42, wherein the LHRH analog is selected from the group consisting of one or more LHRH agonists, one or more LHRH antagonists, and combinations thereof.

47. The kit of claim 42, further comprising at least one cytokine, at least one growth factor, or a combination of at least one cytokine and at least one growth factor.

48. The kit of claim 47, wherein the cytokine is selected from the group consisting of Interleukin 2 (IL-2), Interleukin 7 (IL-7), Interleukin 15 (IL-15), and combinations thereof.

49. The kit of claim 47, wherein the growth factor is selected from the group consisting of members of the epithelial growth factor family, members of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), and combinations thereof.

50. The kit of claim 48, wherein the growth factor is selected from the group consisting of members of the epithelial growth factor family, members of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), and combinations thereof.

51. A method for delivering a sex steroid analog to a patient, comprising:  
laser-irradiating the skin of the patient to create perforations or alterations in the skin,  
and  
20 placing the sex steroid analog on the irradiated skin,  
wherein the sex steroid analog is delivered through the perforations or alterations in the irradiated skin.

52. A method for delivering a sex steroid analog to a patient, comprising:

delivering the sex steroid analog to the skin of the patient, and  
permeabilizing the skin of the patient with high pressure impulse transients,  
wherein the impulse transients cause the sex steroid analog to diffuse through the  
permeabilized skin of the patient.

5 53. A method for enhancing transplantation of donor hematopoietic stem cells into  
the thymus of a recipient patient, comprising:

depleting the T cells of the patient,  
reactivating the thymus of the patient, and  
transplanting donor hematopoietic stem cells to the patient,

10 wherein uptake of the donor hematopoietic stem cells into the patient's thymus is  
enhanced as compared to the uptake that would have otherwise occurred in a patient prior to  
thymus reactivation.

54. A method for increasing virus-specific peripheral T cell responsiveness of a  
patient with an at least partially atrophied thymus, comprising:

15 reactivating the thymus of the patient,  
exposing the patient to a virus,  
determining the virus-specific peripheral T cell responsiveness in the patient,  
wherein the patient has an increased viral-specific peripheral T cell responsiveness as  
compared to the responsiveness that would have otherwise occurred in a patient prior to thymus  
20 reactivation.